Remarks

Claims 46-61 are pending; claims 1-3, 5-6, 8-19, 21-31, and 33-42 are canceled. Reconsideration of the newly added claims in light of the remarks that follow is respectfully requested.

I. Newly added claim

Claim 46 is added directed to an immunological adjuvant composition useful for enhancing the immune response against an active agent. The composition includes a first adjuvant consisting essentially of amorphous calcium phosphate particles and a liquid component. The first adjuvant is formulated as an injectable paste having a solids content of greater than or equal to 40 wt%.

Claim 47 is added directed to an immunological composition useful for enhancing the immune response against an active agent. The composition includes a first adjuvant having amorphous or nanocrystalline calcium phosphate particles and a liquid component. The first adjuvant is formulated as an injectable paste having a solids content of greater than or equal to 40 wt%. The composition also includes an active agent selected from the group consisting of antigens, bacteria or viruses or fragments thereof, haptens, allergens and immunogens.

Methods of inducing an immunological response are also added. No new matter has been added with the newly added claims.

II. Rejection of the claim for obvious-type double patenting.

Claims 1-6, 8-12, and 15-25 stand rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1-11 of co-owned U. S Patent No. 6,214,368. Applicants note that claims 1-6, 8-12, and 15-25 have been canceled with this response and that patentable subject matter has not yet been identified. Applicants will consider the appropriateness of filing a terminal disclaimer once the claims are considered to contain allowable subject matter.

III. Rejection of the claims for indefiniteness

Claims 1-6, 8-12, and 15-25 stand rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The Office Action considers use of the term "a second calcium phosphate" in claim 15 and "strongly" in claims 6 and 19 to be indefinite and vague.

Claims 1-3, 5-6, 8-19, 21-31, and 33-42 have been canceled and the newly added claims 46-61 do not include the subject language. The amendments address the concerns raised in the Action, and the rejection can now be withdrawn.

III. Rejection of the claims over Constantz et al.

Claims 1-6, 8, 15-19, 21, 28-31 and 40-41 stand rejected under 35 U.S.C. § 102(b) as anticipated by Constantz et al (USP 5,782,971). In order to anticipate a claim, the prior art much teach, either explicitly or inherently, each and every limitation of the claimed invention. The Office Action states that the Constantz teaches amorphous calcium phosphate mixtures in combination with a second calcium source such as tetracalcium phosphate in amounts higher than 40 wt% and thereby anticipates the claims. The Office Action also notes that Constantz discloses combination of the composition with proteins.

Newly added claim 46 is directed to a composition "consisting essentially of amorphous calcium phosphate particles and a liquid component, said first adjuvant formulated as an injectable paste having a solids content of greater than or equal to 40 wt%." Constantz discloses a multicomponent composition that includes calcium phosphate sources other than amorphous calcium phosphate. Thus, claim 46 and those dependent thereon are not anticipated by Constantz.

Newly added clam 47 is directed to "an immunological composition useful for enhancing the immune response against an active agent a first adjuvant comprising amorphous or nanocrystalline calcium phosphate particles and a liquid component, said first adjuvant formulated as an injectable paste having a solids content of greater than or equal to 40 wt%; and an active agent selected from the group consisting of antigens, bacteria or viruses or fragments thereof, haptens, allergens and immunogens." There is no teaching in Constantz of combining an amorphous or nanocrystalline calcium phosphate particles with any of the active agent recited in claim 47. Thus, claim 47 and those dependent thereon are not anticipated by Constantz.

Constantz is concerned with bone regeneration and discloses a composition for treatment of injured or compromise hard tissue. The Constantz compositions include amorphous calcium phosphate and *at least one additional* calcium source (and typically there are two or more). There is no teaching or suggestion that such a material is suitable for use as an adjuvant or to enhance the immune response against an active agent. Thus, Constantz neither anticipates nor renders obvious the invention set forth in claims 46-61.

IV. Rejection of the claims over Poser et al.

Claims 1-6, 8, 15-19, 21, 28-31 and 40-41 stand rejected under 35 U.S.C. § 102(b) as anticipated by Poser et al (USP 5,968,253). In order to anticipate a claim, the prior art much teach, either explicitly or inherently, each and every limitation of the claimed invention. The Office Action states that the Poser teaches paste-like flowable compositions including 60-95% tricalcium phosphate, a second calcium phosphate such as monocalcium phosphate monohydrate and an aqueous injectable lubricant.

Newly added claim 46 is directed to a composition "consisting essentially of amorphous calcium phosphate particles and a liquid component, said first adjuvant formulated as an injectable paste having a solids content of greater than or equal to 40 wt%." Poser discloses a multicomponent composition that does not even include amorphous calcium phosphate. Thus, claim 46 and those dependent thereon are not anticipated by Poser.

Newly added clam 47 is directed to "an immunological composition useful for enhancing the immune response against an active agent a first adjuvant comprising amorphous or nanocrystalline calcium phosphate particles and a liquid component, said first adjuvant formulated as an injectable paste having a solids content of greater than or equal to 40 wt%; and an active agent selected from the group consisting of antigens, bacteria or viruses or fragments thereof, haptens, allergens and immunogens." There is no teaching in Poser of combining an amorphous or nanocrystalline calcium phosphate particles with any of the active agent recited in claim 47. Thus, claim 47 and those dependent thereon are not anticipated by Poser.

Poser is concerned with inclusion of an antimicrobial agent into calcium phosphate compositions useful in orthopedic and dental applications. There is no teaching or suggestion that such a material is suitable for use as an adjuvant or to enhance the immune response against

an active agent. Thus, Poser neither anticipates nor renders obvious the invention set forth in claims 46-61.

V. Rejection of the claims under 103(a).

Claims 1-3, 5-6, 8, 10-14, 17-18, 23-27, 39, and 43-44 stand rejected under 35 U.S.C. §103(a) as unpatentable over Relyveld (U.S. Patent No. 4,016,252), in view of Amerongen *et al.* (U.S. Patent No. 5,443,832) and Constantz *et al.* (U.S. Patent No. 5,782,971).

The references are relied upon as stated in a previous Office Action (see, Paper No. 15).

Relyveld is relied upon to teach vaccine formulations using calcium phosphate gels (< 3.3 wt%) having a calcium to phosphorous ratio of 1.62 to 1.85. The Office Action admits that Relyveld does not teach a 40 wt% solids adjuvant composition.

Amerongen is relied upon to teach the use of hydroxyapatite in amounts higher than 40 wt% to elicit an immune response in mammals. Applicants have repeatedly objected to the characterization of the prior art, namely, **Amerongen does not disclose hydroxyapatite compositions having a solids content of greater than 40 wt%.**

The Office Action correctly notes that Example 2 discloses the suspension of 1 mg hydroxyapatite into 200 μL PBS buffer; however, the Office Action incorrectly concludes that this composition has a weight % solids of greater than 40 wt%. A step-by-step analysis of determination of solids content is described below.

For the purpose of this discussion, we assume that the PBS buffer has a density approximating that of water. The density of water at room temperature is 0.997 g/mL, as is established in the Table accompanying this Response as Exhibit 1. The relationship between milliliter (mL) and microliter (μL) is:

$$1\ \mu L = 1 \times 10^{-3}\ mL = 1 \times 10^{-6} L$$

This allows one to express 200 microliters in milliliters as follows:

$$200\mu L * 1\times10^{-3}\frac{mL}{\mu L} = 0.2mL,$$

and to express the weight of 200 microliters solution as follows:

$$0.2mL * 0.997\frac{g}{mL} = 0.1994g\,.$$

Thus, 1 mg (or 0.001g) of hydroxyapatite powder is introduced into 0.1994 g of PBS buffer for a total weight of 0.2004 g (0.1994 g liquid, plus 0.001 g powder). The solids content is determined by the following equation:

$$wt\%solids = \frac{weightsolids}{totalweight} \times 100\% = \frac{0.001}{0.2004} = 0.499wt\%$$

Thus, the suspended hydroxyapatite composition of Amerongen contains no more than 0.5 wt% solids. If the Office nonetheless disagrees with this analysis, Applicants request that the Office provide a specific and detailed explanation as to how Amerongen teaches a greater than 40 wt% solids composition.

Constantz is relied upon to disclose a multicomponent self-setting cement that includes amorphous calcium phosphate as a minor component of the cement. Constantz indicates that it is possible to modify the viscosity of the composition by varying the solids content of the composition; however, such modification does not contemplate a solids content range over two order of magnitudes. Indeed, Constantz discloses that the liquid can range from about 15 to 70 weight percent of the total composition (col. 5, l. 47).

Constantz states that the utility of the disclosed calcium phosphate cement is for

> connective tissue replacement, including bone cement, an injected prosthetic implant, a prosthetic orthopaedic or dental implant, as a root canal filler, a prophylactic injection to augment weak osteoporotic bone, to fill voids resulting from fracture reduction, or a vehicle for drug delivery. The composition may be used as a paste, being applied to a surface for adherence or holding some structure in place. For example, the cement composition may be used to fixate prosthetic devices into regions of bone, as a means of bonding fracture bone fragments together, and the like.

Col. 6, l. 56-67.

Constantz further contemplates the addition of other ingredients such as:

> "organic polymers, e.g., proteins, including bone associated proteins which impart a number of properties, such as enhancing resorption, angiogenesis, cell entry and proliferation,

> mineralization, bone formation, growth of osteoclasts and/or osteoblasts, and the like, where specific proteins of interest include osteonectin, bone sialoproteins (Bsp), .α-2HS-glycoproteins, bone Gla-protein (Bgp), matrix Gla-protein, bone phosphoglycoprotein, bone phosphoprotein, bone proteoglycan, protolipids, bone morphogenic protein, cartilage induction factor, platelet derived growth factor, skeletal growth factor, and the like; particulate extenders; inorganic water soluble salts, e.g. NaCl, calcium sulfate; sugars, e.g. sucrose, fructose and glucose; pharmaceutically active agents, e.g. antibiotics; and the like..."

(Col. 5. l. 62 – Col. 6, l. 8).

The Office Action relies upon these passages to teach the use of the Constantz material as a high solids content adjuvant composition.

The Office Action argues that it would have been obvious to modify the low solids content composition of Relyveld to form a hardenable calcium phosphate composition. The Office Action then points to Amerongen to teach a high solids content in an adjuvant composition and Constantz to teach an amorphous calcium phosphate as a suitable drug delivery vehicle as a basis for this motivation. This analysis fails on several points.

As discussed in detail above, Amerongen fails to disclose a greater than 40 wt% composition. Rather it discloses a 0.5wt% solids suspension – a composition having **a solids content two orders of magnitude less than the claimed composition**. Not only do Relyveld and Amerongen fail to disclose the desirability of an adjuvant that is a paste having a solids content of greater than 40 wt%, but they teach that a calcium phosphate adjuvant should be orders of magnitude more dilute.[1] The resultant adjuvants are waterlike and disperse rapidly in the host. These characteristics contrast sharply to those of the pastelike (but injectable) adjuvant composition of the present invention, which are of sufficient viscosity to form a depot after injection for retention within the host[2]. The instant adjuvant compositions provide the capability for a sustained immunogenic response, which may be desirable in some vaccine circumstances.

In addition, Constantz fails to suggest that the calcium phosphate paste has any utility other than in a bone setting. Constantz teaches that the composition is useful in the treatment of

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[1] All of the compositions disclosed in Relyveld or Amerongen have at most 3 wt%, and typically much lower, solids content.

[2] Note that hardening is not required.

bone, where a high solids content material clearly is required to fill a bone site and provide the desired bone mass after healing. There is no teaching or suggestion that similar high solids pastes would find utility in applications where high solids content typically is not desired or required by the prior art.

The disclosed additives in Constantz all relate to bone treatment and are added to a materials formulated as a bone cement. The sole brief reference to a drug delivery vehicle must be read in light of the specification to mean drug delivery at bone treatment sites. Even if the teaching of Constantz were construed to include drug delivery at sites outside of bone sites (with which we disagree), such a teaching is still irrelevant to the claimed invention, which is directed to an adjuvant for enhancing an immune response and not an inert carrier for delivering an active agent.

Furthermore, there is no teaching or suggestion that the calcium phosphate materials of Constantz have any immunogenic effects. Since the materials and material combinations taught by Constantz (reactive multicomponent calcium phosphates) differ from those of the claimed invention (single component amorphous calcium phosphates, and nanocrystalline calcium phosphates), there is no reason to expect that the compositions taught by Constantz are inherently immunogen.

Thus, an isolated teaching of a calcium phosphate composition having a solids content of greater than 40 wt% is taken out of context from Constantz's teaching as a whole, namely that a multicomponent paste containing a minor amount of amorphous calcium phosphate and other calcium and calcium phosphate sources is useful as a hardening bone cement. There is no motivation to combine a reference directed to a bone substitute material, in which the calcium phosphate is remodeled into bone, with references that call for a low solids content, aqueous suspension of a single form of calcium phosphate for use as an adjuvant.

For the forgoing reasons, it is submitted that the claims are patentable over the cited art.

VII. Rejection of the claims under 35 U.

Claims 9, 22, 28-31, 33, 34-38, and 40-42 stand rejected under 35 U.S.C. §103(a) as unpatentable over Relyveld (U.S. Patent No. 4,016,252), in view of Amerongen *et al.* (U.S.

Patent No. 5,443,832) and Constantz *et al.* (U.S. Patent No. 5,782,971), and further in view of Gupta *et al.* (Vaccine Design, Ch. 8, pp. 229-248 (1995)) or Kossovsky *et al.* (U.S. Patent No. 5,462,751).

The primary and secondary references fail to disclose the claimed invention for the reasons set forth in section VI, above. The additional tertiary references Gupta and Kossovsky fail to provide a teaching or suggestion of the claimed invention. Thus, claims 46-60 are patentable over the combination of Relyveld, in view of Amerongen and Constantz, and further in view of Gupta or Kossovsky.

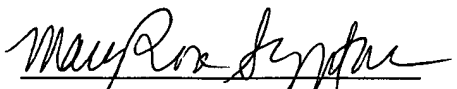
VIII. Conclusion

Applicants submit that the amended claims, in light of the above remarks, place the application in condition for allowance. A favorable Notice to that effect is respectfully requested. The Examiner is requested to contact the undersigned to facilitate further prosecution of the application.

Should a fee be required regarding this matter, the Commissioner is authorized to charge the appropriate fee to Deposit Account No. 08-0219.

Respectfully submitted,

Dated: March 11, 2003



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North Carolina State University

Density of Water
Vapor Pressure of Water

Temperature	Density	Vapor Pressure
°C	g/mL	torr
15	0.9991026	12.79
16	0.9989460	13.64
17	0.9987779	14.54
18	0.9985986	15.49
19	0.9984082	16.49
20	0.9982071	17.55
21	0.9979955	18.66
22	0.9977735	19.84
23	0.9975415	21.09
24	0.9972995	22.40
25	0.9970479	23.78
26	0.9967867	25.24
27	0.9965162	26.77
28	0.9962365	28.38
29	0.9959478	30.08
30	0.9956502	31.86

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EXHIBIT 1